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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,131	02/13/2002	Babu J. Mavunkel	219002028310	9859

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EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,131	MAVUNKEL ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-71 and 75-78* is/are rejected.

7)☒ Claim(s) *72-74 and 79* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a RCE of SN 10/076,131. The after final amendment dated September 19, 2005 filed with the RCE and remark have been entered. Claims 1-38 have been canceled. Claims 39-78 are pending.

The version of specification received by the PTO dated Aug. 8, 2003 which has been verified by the attorney of record is now the copy of specification under consideration.

2. Claims 39, 75-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39, the term R4 is "alkyl and aryl optionally including one or more heteroatoms selected from O,S and N" is indefinite and unclear. What does including mean? Heteroaromatic? Or substituted with heteroatom containing moiety? it is unclear of what chemical structure is this term referring to. A Declaration under 37 CFR 1.132 by Mavunkel stated that the term "including one or more heteroatoms" are describing structure of hydrocarbon wherein the backbone or skeleton of the moiety is replaced by one or more heteroatom. Such declaration further support the ambiguity of the terms and the propriety of the rejection. Were the structure limited to alkyl including heteroatoms replacing a carbon atom of the backbone, then, the particularity of such structure has not been pointed out as described by the declaration. Further, no antecedent basis for such description can be found in the specification.

Claims 75-78 are very confusing. Please note that in the base claim 75, a disease of "heart or brain failure(stroke) that are characterized by ischemia and reperfusion injury" was named. In the dependent claim 76 the condition of "ischemic/reperfusion injury" was claimed. Is this further limiting of the base claim? Please note that the base claim is limiting ischemia and reperfusion injury to resulting in heart or brain failure while the dependent claim seems to broadening the condition. Claim 77 is drawn to method of treating condition associated with cardiac failure. In the dependent claim 78, said heart condition was limited to "....vasculitis, vascular restenosis, valvular disease....". The definition of heart failure and vaculitis from the

Merck Mannuel is hereby attached. Please note that none of the condition for heart failure included vasculitis and vasculitis is normally known as a blood vessel disease Please note that clinically, proinflammatory response is not inflammation (see Cecil textbook of medicine, disorders of inflammatory response recited in PTO-892 07/26/04). The scope of the claims are very confusing. The above delineation are mere examples of the self conflicting scope of the claims and not an exhausted listing. Applicants are urged to consult medical textbooks, Merck manuals etc. for definition of diseases/pathology and clearly delineate what has been described and what conditions are further limitation of broad terms.

3. Claims 39-71, 75-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention or; the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims limiting the compounds to X^1 is CO, SO or CHOH, and X^2 is CH, CH_2, CO, CHON, SO or SO_2 lacks antecedent basis and are NEW MATTER. Please note that the particular subgeneric scope as now claimed lacks antecedent basis in the specification. Further based on the description of page 5, line 14, that "X^2 may be any of the alternatives set forth above for X^1", the particular amendment specifically set forth a subset of combination of the two Markush elements is a teaching away from the description of the specification.

Removal of NEW MATTER is required. In re Russmussen 210 USPQ 325.

As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of invention

The scope of claim 1 wherein R4 is "alkyl and aryl optionally including one or more heteroatoms selected from O,S and N" lacks sufficient descriptive and enabling support in the specification. No explicit description can be found as to what the intended chemical structure is for such terms. The art rejections which will follow this rejection are based on the broadest interpretation of the terms.

The method of treating disease as currently amended in claims 75-78 contains incredible utility. That is for a single compound to be able to treat such diversity of diseases as named in claim 75 is incredible. No nexus was found between the compound and such vast array of diseases nor was any nexus evidenced by the art that method of treating the claimed disease such as heart failure includes P38 kinase inhibitors (see Merck manual on drug for treating heart failure).

The state of the art and predictability

The state of the art indicated that the substituents on the bicyclic moieties are important features independently and distinct responsible for the utility of the chemical products. For example, it is evidenced that when R4 is aryl including four nitrogen, the compounds have activity in treating proliferative disease (CA 139:117268). When the substituents on the bicyclic ring wherein R4 is hydrogen, X1 is sulfonyl (CA 131:67650), the compounds have thrombin inhibition activity. Therefore, the drastic diversity in utility resulted from small chemical structure all falling within the claimed scope indicated the high degree of unpredictability of such compounds.

In so far as the compounds having P38 kinase inhibiting activity is concerned, the specification has described that the acitivity for the kinase in a subject is through the cytokine regulatory system (see p.18). Function of cyctokine has been recognized in the art to be highly complexed and there is only limited understanding of the mechanism that lead to one activity over another when a specific cyctokine is involved in a specific biological reaction (see CA 125:31527) that is no generalization can be extrapolated from such mechanism. In absence of any linkage of the particular enzyme inhibiting activity inexorably with any specific physiological function, the specification provided insufficient description to the currently amended scope.

In so far as the method of treating disorder of the claims is concerned, it is well known in the art for treating eye inflammation i.e. uveitis, the ordinary route of administration is topical. For treating CNS disorder such as cerebral malaria, the drug must pass through the blood brain barrier. No description on dosage or site of administration for such diversity of method as found in claims 75-78 finds description or enabling evidence in the specification.

The amount of guidance and working examples

A survey of the specification revealed that none of the X1 is sulfonyl compounds has been made or tested to have p38 kinase activity. None of the compounds wherein R4 is broadly "aryl" including heteroatoms has been made or tested to have p38 kinase activity.

In view of the diversity of utility based on the bicyclic core with distinct substitution as evidenced supra, the lacking of variation for the Markush scope with such breadth finds the

claimed scope lacks description as well as enablement. Especially, it is unclear of what is the claimed scope as delineated under the rejection under 35 USC 112 2nd paragraph supra.

In addition, were applicants' proinflammatory response including diseases such as arthritis, a 102(f) or (g) issue may have to be resolved with the CA 139:117268 reference (see citation of PTO-892 07/26/04).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-58, 75-78 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by Daun et al. US 2005/0124649.

Please note that the instant specification disclosed no compounds wherein R4 is aryl optionally including one or more heteroatoms selected from O,S and N. Therefore, the Daun et al. reference which disclosed heteroaryl moiety compounds anti-dated the instant specification and constituted a provisional 102(e), see compounds at page 25 compound #53, p.26, compound #54, 55, page 33 compound #92, 94 which anticipated the instant claims for treating inflammatory and proliferative diseases (see page 1).

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-58 are rejected under 35 U.S.C. 102(a) or (b) as being clearly anticipated by Domiguez et al. CA 131:67650, Cook et al. CA 132:347492 .

See CA 131:67650 RN 228552-27-0, CA132:347492 RN268730-34-3.

This rejection of the previous office action is maintained when the new matter is removed from the claims and the claims are reversed to the previous version containing structure of "isosteres" of CO or CH2

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domiguez et al. CA 131:67650, Cook et al. CA 132:347492 or Kalihana et al. CA 135:313624 in view of King (medicinal Chemistry) or Patani et al.

Determination of the scope and content of the prior art (MPEP §2141.01)

The primary references disclosed structurally analogous compounds, see CA 131:67650 RN 228552-27-0, CA132:347492 RN268730-34-3 or CA 135:313624 RN 367508-34-7, 367509-01-1, 367510-05-2 i.e. RN 367509-01-1 position isomer being taught by RN 367508-34-7 or RN 367510-05-2 that changing position is obvious.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the delineated compounds supra is that instead of X^1 is CO, SO or CHOH, and X^2 is CH, CH_2, CO, CHON, SO or SO_2, the prior art compounds contain X^1 or X^2 being isostere of the claimed structure. King disclosed variations of isosteric linker for CO or CH2 being SO or NH, while Patani et al. provided motivation that isosteric modification of a known compound is the rational approach for drug design.

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references places the proven compounds and the rational approach in modification in the possession of artisan in the field. One having ordinary skill in the art would be motivated to modify the prior art compounds with the known isosteric replacement of the linkers **because** such modification is rational and is expected to produce more useful drugs for a lead compound.

8. Claims 72-74, 79 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Dec. 2, 2005

Celia Chang
Primary Examiner
Art Unit 1625